Combination Therapy for Human Immunodeficiency Virus-Associated Cryptococcal Meningitis: Whom, When, and Where?

Correspondence

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To the editor—We appreciate the thoughtful comments raised by Wolbers and Day [1] in response to our article [2]. We agree with their primary point—that our meta-analysis summarized data across studies, and it is therefore best suited to evaluate study-level and not individual-level predictors of outcomes. We should have specified more clearly that our analysis is best suited for drawing inferences about relationships among patient populations, but not about individual patients. Indeed, this point is true for almost all meta-analysis, and it also applies to most individual randomized trials [3].

It is important to note that we did not intend to imply that combination amphotericin B and flucytosine conferred a benefit in patients with cryptococcal meningitis with altered mental status. Rather, in our meta-analysis, we were unable to identify a statistically significant treatment benefit across all published literature, for combination amphotericin B with flucytosine over amphotericin B alone. Although there was some implication of a benefit from adjunctive flucytosine in a subanalysis limited to studies that included patients with altered levels of consciousness, this estimate was not statistically significant (odds ratio = 0.56; 95% confidence interval [CI], .23–1.43) (Figure 1). As such, we hypothesized in the discussion that populations with altered consciousness might be more likely to benefit from adjunctive flucytosine therapy. If this hypothesis were correct, it would require patient-level data for confirmation.

In their recent large, randomized trial, Day et al [4] demonstrated superiority of combination amphotericin B and flucytosine over amphotericin B alone at 10 weeks. They now present a subanalysis with patient-level data that suggests that those with a normal Glasgow Coma Score (GCS) appeared to derive as much benefit (if not more) from the addition of flucytosine as those with a GCS < 15. Although their study was not powered to detect differences in these subgroups, their data do lend support to the use of flucytosine in individual patients with normal mental status within their study population. It should be noted that the overall mortality in their study was 36% at 10 weeks (and 30% among those who received amphotericin B and flucytosine combination therapy). In contrast, the only other large randomized trial to compare amphotericin B alone with amphotericin B and adjunctive flucytosine found no difference in mortality between groups at 10 weeks (6.7% versus 6.9%; relative risk = 0.97; 95% CI, .46–2.04) [5]. It is noteworthy that this other study was conducted in the United States, excluded comatose patients from enrollment, and had a lower prevalence of participants with altered mental status than the Day et al [4] study (11% vs 28%).

We believe that the contrasting data from these 2 studies are in line with our overall conclusion: that current available evidence suggests that the adjunctive use of flucytosine might be beneficial in populations with advanced disease who are at high overall risk for mortality. As Wolbers and Day [4] point out, this does not necessarily mean that patients with normal mental status will not benefit from adjunctive flucytosine, only that populations with low overall risk of mortality are less likely to

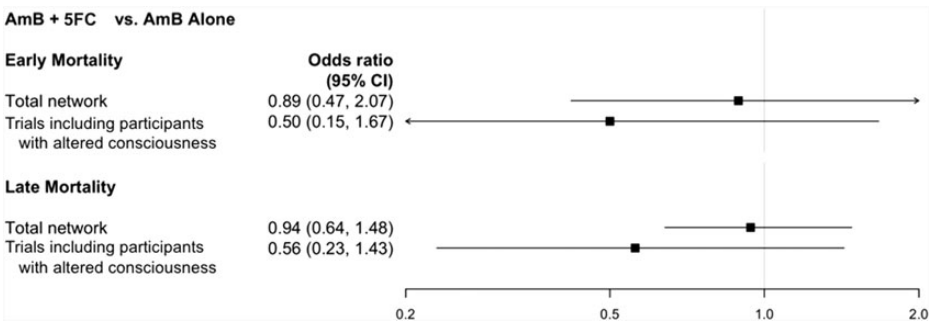

Figure 1. Forrest plot from network meta-analysis comparing odds of early (2-week) and late (10-week) mortality between combination amphotericin B and flucytosine with amphotericin B alone for human immunodeficiency virus-associated cryptococcal meningitis. Abbreviations: AmB, amphotericin B; 5FC, flucytosine; CI, confidence interval.

benefit. Unfortunately, for the time being, it appears that flucytosine is largely only available and in use in the areas of the world where the current data suggest it has the least benefit, whereas populations with the highest mortality often cannot access it [6, 7]. Indeed, the most important conclusion we draw from our study is that more data is required, across a range of patient populations and disease stages, to elucidate which drugs are needed for which patients, and to ensure that the optimal therapies are available to those who need them.

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